

Synthesis of nitrogen-containing dispiroheterocycles (1) using nitrilimines

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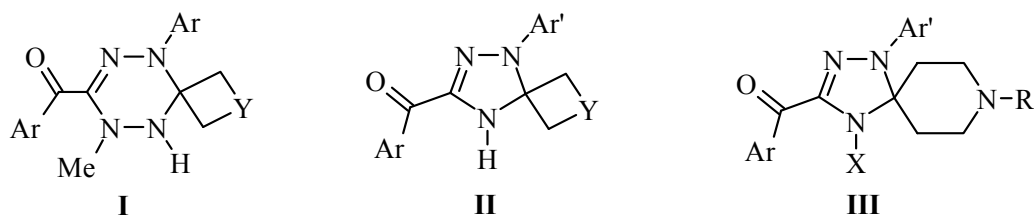
Abstract

A novel series of 1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-dienes **4a-k** were synthesized by the reaction of 1,4-cyclohexanedione methylhydrazone **3** with appropriate nitrilimines **2**. The microanalysis and the spectral data of the synthesized compounds are in full agreement with their molecular structure.

Keywords: Nitrilimines, 1,4-cyclohexanedione methylhydrazone, dispiroheterocycles

Introduction

In recent years, attention has been increasing regarding the synthesis of spiroheterocyclic compounds which exhibit various biological activities,¹⁻⁸ pharmaceutical^{9,10} and antitumor properties.^{11,12} Nitrilimines are well explored dipoles and their reactions for the construction of heterocyclic systems are known to proceed *via* 1,3-dipolar cycloaddition with multiple bonds, cyclocondensation with nucleophilic substrates and 1,3-electrophilic addition with nucleophiles. Examples of these modes of reactions were recently reviewed by Ferwanah *et al.*¹³ for the reactions of hydrazones and oximes with nitrilimines and nitrile oxides. The synthesis of different spiroheterocycles **I-III** was recently reported using nitrilimines and cycloalkanone hydrazones or oximes¹⁴⁻¹⁷ (Figure 1). As part of our program aimed at developing new biologically active compounds, we report here the synthesis of the hitherto unknown dispiroheterocyclic compounds **4a-k** from the reaction between different nitrilimines **2** and 1,4-cyclohexanedione methylhydrazone **3**.

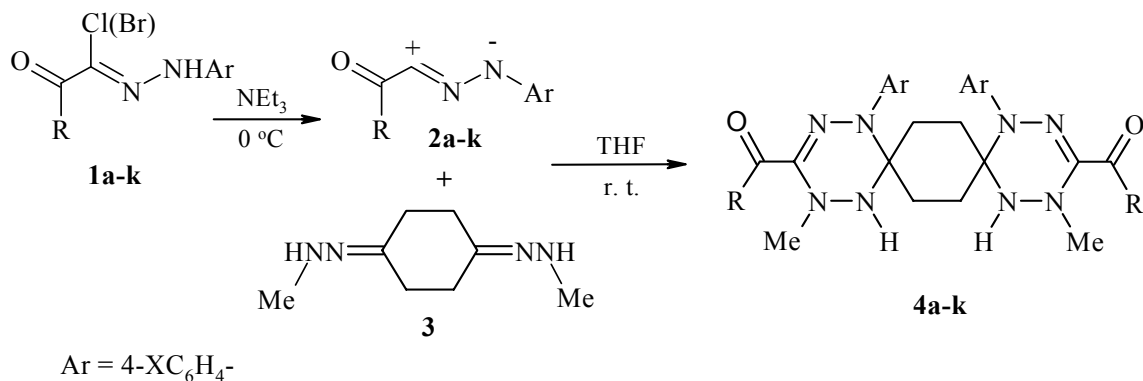


Ar = Ph-, 2-C₁₀H₇-, 2-C₄H₃O-, 2-C₄H₃S-, PhNH-; R = -Me, -CHMe₂, -CH₂Ph; X = -H, -NHCOPh
 Y = -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -CH₂CHMeCH₂-, -CH₂CH(t-Bu)CH₂-

Figure 1

Results and Discussion

The hydrazoneyl halides **1a-k** were prepared by a modified literature procedure,¹⁸⁻²² and the nitrilimines **2** were generated *in situ* from **1** by reaction with triethylamine (Et₃N). The non-isolable nitrilimines **2** reacted readily with 1,4-cyclohexanedione methylhydrazone **3** affording the corresponding 1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-dienes **4a-k** (Scheme 1), owing to the high nucleophilicity of the nitrogen atom carrying the methyl group. The formation of compounds **4a-k** involving the nucleophilic addition of the methyl hydrazone **3** to the nitrilimines **2** to give the non-isolable acyclic intermediates **5**, which ultimately undergo intramolecular cyclization to dispiroheterocyclic compounds **4a-k** (Scheme 2).

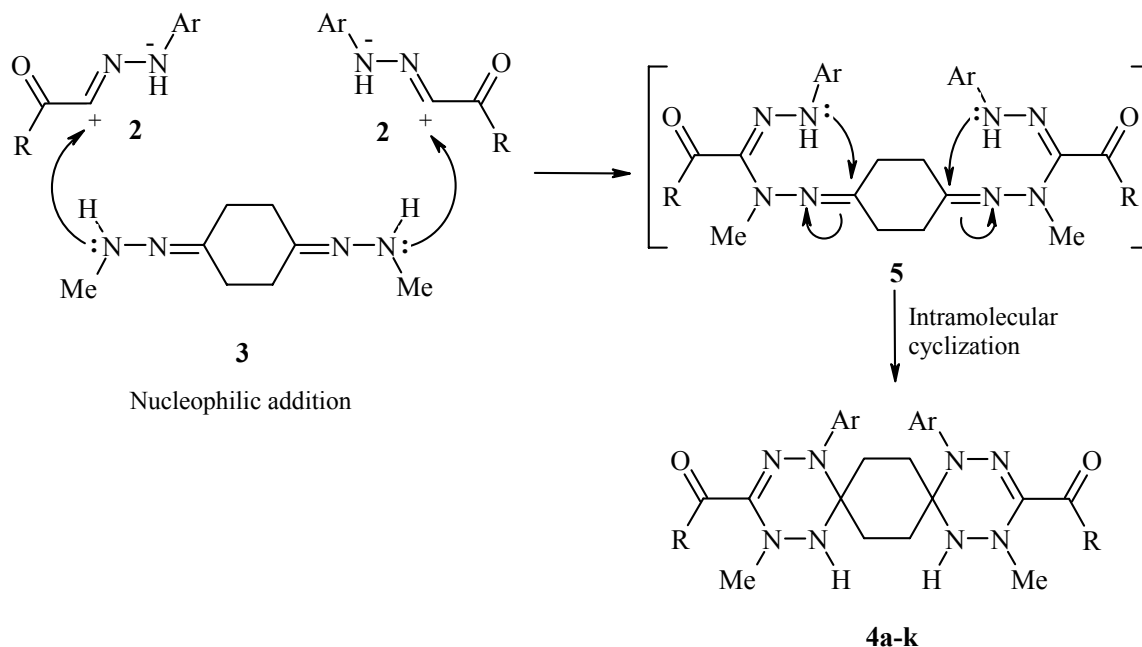


Entry	a	b	c	d	e	f	g	h	i	j	k
R	Me	Me	MeO	Ph-	PhNH-	PhNH-	PhNH-	2-C ₁₀ H ₇ -	2-C ₁₀ H ₇ -	2-C ₄ H ₃ O-	2-C ₄ H ₃ S-
X	Cl	Br	Cl	Cl	H	Cl	Br	H	Cl	Cl	Cl

Scheme 1. Synthetic pathway for dispiro compounds **4a-k**.

Spectral data analysis

The structures of compounds **4a-k** were established based on the basis of their elemental analysis and spectroscopical data. Physical properties, molecular ion peaks and elemental analysis for these triazinones are presented in the experimental section. The electron impact (EI) mass spectra displayed the correct molecular ions in accordance with the suggested structures. Their IR spectra showed absorption bands in the region $3280\text{-}3250\text{ cm}^{-1}$ and $1660\text{-}1640\text{ cm}^{-1}$ assignable to NH and carbonyl group, respectively. Their ^1H NMR spectra revealed, besides aromatic protons at $8.5\text{-}7.1$ ppm and singlet signal at $3.2\text{-}3.0$ ppm assigned to NCH_3 protons and D_2O -exchangeable singlet signal in the region $5.7\text{-}5.6$ ppm assignable to the ring NH proton. The detailed ^1H NMR data is shown in the experimental section. Their ^{13}C NMR spectra showed all the signals corresponding to the proposed structures, especially C-6 and C-9 (spiro carbons) were found to resonate at about $75\text{-}70$ ppm. This is similar to reported values of spiro carbons flanked by two nitrogen atoms in six-membered heterocycles,^{14,22} which provide strong evidence in support of the structures **4a-k**. The complete ^{13}C NMR data are presented in experimental section.



Scheme 2. The suggested reaction mechanism for compounds **4a-k**.

Biological activity

Most of the newly synthesized compounds **4a-k** were tested for their antibacterial and antifungal activity *in vitro* against bacterial strains such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella spp*, *Proteus spp*, *Pseudomonas* and *Aspergillus flavus*, *Candida albicans* as fungi, employing the nutrient agar disc diffusion method²³ at (1-10 mg/ml) in dimethyl formamide (DMF) by measuring the inhibition zone in mm. It is interesting to note that these

dispiroheterocycles **4a-k** showed weak degree of activity against tested bacteria and fungi in comparison to DMF which was used as control. That may due to lack active substituted groups.

Experimental Section

General Procedures. All melting points were determined on an A. Krüss Melting Point Meter equipped with a digital thermometer and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO- d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analysis was performed at Cairo University, Egypt. The hydrazonoyl halides **1a-k**¹⁸⁻²² and 1,4-cyclohexanedione methylhydrazone **3**²⁴ were prepared according to literature procedures. Tetrahydrofuran (THF) and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

Reaction of nitrilimines **2** with 1,4-cyclohexanedione methylhydrazones **3**

Triethylamine (0.05 mol, 7 ml) in tetrahydrofuran (10 ml) was added dropwise to stirred mixture of a hydrazone **3** (0.02 mol) and the appropriate hydrazonoyl halides **1a-k** (0.01 mol) in tetrahydrofuran (70 ml) at -5-0 °C. The reaction temperature was allowed to rise slowly to ambient temperature and stirring was continued for 4-6 hours. The precipitated triethylammonium salt was filtered off and the solvent was then evaporated. The residue was washed with water (100 ml) and in few cases the gummy products were triturated with ethanol (10 ml). The crude solid product was collected and recrystallized from ethanol to give the desired compounds. The following compounds were synthesized using this method:

3,12-Diacetyl-1,14-di(4-chlorophenyl)-4,10-dimethyl-1,2,4,5,10,11,13,14-octaazadispiro-[5.2.5.2]hexadeca-2,12-diene (4a). Yield 57%, m.p. 139-141 °C. IR (KBr): cm^{-1} 3285 (NH), 1682 (C=O), 1622 (C=N). ^1H NMR (DMSO- d_6): δ /ppm: 8.52-7.25 (m, 8H, arom. protons), 5.74 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.56 (s, 6H, 2CH₃), 2.10-1.83 (m, 8H, 4CH₂). ^{13}C NMR (DMSO- d_6): δ /ppm 187.10 (C=O), 143.90-126.10 (C=N, arom. carbons), 75.10 (spiro carbons), 43.45 (NCH₃), 28.07, 26.83 (2CH₂). MS: m/z = 556/558 (M^+ , Chlorine isotopes). Anal. for C₂₆H₃₀Cl₂N₈O₂ (557.49): Calcd. C, 56.02; H, 5.42; N, 20.10%. Found: C, 56.20; H, 5.60; N, 19.90%.

3,12-Diacetyl-1,14-di(4-bromophenyl)-4,10-dimethyl-1,2,4,5,10,11,13,14-octaazadispiro-[5.2.5.2]hexadeca-2,12-diene (4b). Yield 55%, m.p. 158-160 °C. IR (KBr): cm^{-1} 3285 (NH), 1681 (C=O), 1620 (C=N). ^1H NMR (DMSO- d_6): δ /ppm 8.52-7.25 (m, 8H, arom. protons), 5.74 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.57 (s, 6H, 2CH₃), 2.10-1.83 (m, 8H, 4CH₂). ^{13}C NMR (DMSO- d_6): δ /ppm 187.10 (C=O), 143.90-126.10 (C=N, arom. carbons), 75.15 (spiro carbons), 43.55 (NCH₃),

28.10, 26.86 (2CH₂). MS: $m/z = 646/648$ (M⁺, Bromine isotopes). Anal. for C₂₆H₃₀Br₂N₈O₂ (646.39): Calcd. C, 48.31; H, 4.68; N, 17.34%. Found: C, 48.80; H, 4.50; N, 17.20%.

1,14-Di(4-chlorophenyl)-4,10-dimethyl-3,12-dimethoxycarbonyl-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4c). Yield 48%, m.p. 137-139 °C. IR (KBr): cm⁻¹ 3280 (NH), 1720 (C=O), 1625 (C=N). ¹H NMR (DMSO-d₆): δ/ppm 8.52-7.25 (m, 8H, arom. protons), 5.74 (s, 2H, 2NH), 3.76 (s, 6H, 2OCH₃), 3.05 (s, 6H, 2CH₃), 2.10-1.83 (m, 8H, 4CH₂); ¹³C NMR (DMSO-d₆): δ/ppm 156.32 (O-C=O), 143.40-124.99 (C=N, arom. carbons), 74.92 (spiro carbons), 53.75 (OCH₃), 43.23 (NCH₃), 27.16, 26.52 (2CH₂). MS: $m/z = 588/590$ (M⁺, Chlorine isotopes). Anal. for C₂₆H₃₀Cl₂N₈O₄ (589.49): Calcd. C, 52.98; H, 5.13; N, 19.01%. Found: C, 52.70; H, 5.00; N, 18.90 %.

3,12-Dibenzoyl-1,14-di(4-chlorophenyl)-4,10-dimethyl-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4d). Yield 51%, m.p. 192-194 °C. IR (KBr): cm⁻¹ 3265 (NH), 1660 (C=O), 1618 (C=N). ¹H NMR (DMSO-d₆): δ/ppm 8.52-7.25 (m, 18H, arom. protons), 5.74 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.10-1.83 (m, 8H, 4CH₂). ¹³C NMR (DMSO-d₆): δ/ppm 187.10 (C=O), 143.90-126.10 (C=N, arom. carbons), 71.45 (spiro carbons), 43.10 (NCH₃), 27.30, 26.76 (2CH₂). MS: $m/z = 680/682$ (M⁺, Chlorine isotopes). Anal. for C₃₆H₃₄Cl₂N₈O₂ (681.63): Calcd. C, 63.44; H, 5.03; N, 16.44%. Found: C, 63.30; H, 4.90; N, 16.35%.

4,10-Dimethyl-1,14-diphenyl-3,12-diphenylaminocarbonyl-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4e). Yield 53%, m.p. 176-178 °C. IR (KBr): cm⁻¹ 3275, 3250 (NH), 1650 (C=O), 1615 (C=N). ¹H NMR (DMSO-d₆): δ/ppm 9.30 (s, 2H, 2PhNH), 7.80-7.06 (m, 20H, arom. protons), 5.68 (s, 2H, 2NH), 3.06 (s, 6H, 2CH₃), 2.13-1.63 (m, 8H, 4CH₂). ¹³C NMR (DMSO-d₆): δ/ppm 158.60 (C=O), 143.90-126.10 (C=N, arom. carbons), 70.55 (spiro carbons), 42.90 (NCH₃), 27.50, 26.90 (2CH₂). MS: $m/z = 642$ (M⁺). Anal. for C₃₆H₃₈N₁₀O₂ (642.77): Calcd. C, 67.27; H, 5.96; N, 21.79%. Found: C, 67.00; H, 6.20; N, 21.80%.

1,14-Di(4-chlorophenyl)-4,10-dimethyl-3,12-diphenylaminocarbonyl-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4f). Yield 50%, m.p. 163-165 °C. IR (KBr): cm⁻¹ 3270, 3255 (NH), 1655 (C=O), 1612 (C=N). ¹H NMR (DMSO-d₆): δ/ppm 9.10 (s, 2H, 2PhNH), 7.82-7.10 (m, 18H, arom. protons), 5.67 (s, 2H, 2NH), 3.06 (s, 6H, 2CH₃), 2.11-1.60 (m, 8H, 4CH₂). ¹³C NMR (DMSO-d₆): δ/ppm 158.80 (C=O), 143.90-126.10 (C=N, arom. carbons), 70.60 (spiro carbons), 42.90 (NCH₃), 27.70, 26.96 (2CH₂). MS: $m/z = 710/712$ (M⁺, Chlorine isotopes). Anal. for C₃₆H₃₆Cl₂N₁₀O₂ (711.66): Calcd. C, 60.76; H, 5.10; N, 19.68%. Found: C, 60.55; H, 4.85; N, 19.60%.

1,14-Di(4-bromophenyl)-4,10-dimethyl-3,12-diphenylaminocarbonyl-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4g). Yield 51%, m.p. 181-183 °C. IR (KBr): cm⁻¹ 3275, 3252 (NH), 1651 (C=O), 1610 (C=N). ¹H NMR (DMSO-d₆): δ/ppm 9.20 (s, 2H, 2PhNH), 7.82-7.10 (m, 18H, arom. protons), 5.65 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.12-1.62 (m, 8H, 4CH₂). ¹³C NMR (DMSO-d₆): δ/ppm 158.80 (C=O), 143.80-126.00 (C=N, arom. carbons), 70.62 (spiro carbons), 42.92 (NCH₃), 27.68, 26.94 (2CH₂). MS: $m/z = 800/802$ (M⁺, Bromine isotopes). Anal. for C₃₆H₃₆Br₂N₁₀O₂ (800.56): Calcd. C, 54.01; H, 4.53; N, 17.50%. Found: C, 53.95; H, 4.65; N, 17.60%.

4,10-Dimethyl-3,12-di(2-naphthoyl)-1,14-diphenyl-1,2,4,5,10,11,13,14-octaazadispiro-[5.2.5.2]hexadeca-2,12-diene (4h). Yield 53%, m.p. 188-190 °C. IR (KBr): cm^{-1} 3265 (NH), 1645 (C=O), 1605 (C=N). ^1H NMR (DMSO- d_6): δ /ppm 8.50-7.22 (m, 24H, arom. protons), 5.72 (s, 2H, 2NH), 3.07 (s, 6H, 2CH₃), 2.12-1.84 (m, 8H, 4CH₂). ^{13}C NMR (DMSO- d_6): δ /ppm 186.62 (C=O), 143.21-125.00 (C=N, arom. carbons), 70.10 (spiro carbons), 43.33 (NCH₃), 27.35, 26.78 (2CH₂). MS: m/z = 712 (M^+). Anal. for C₄₄H₄₀N₈O₂ (712.86): Calcd. C, 74.14; H, 5.66; N, 15.72%. Found: C, 74.30; H, 5.75; N, 15.61%.

1,14-Di(4-chlorophenyl)-4,10-dimethyl-3,12-di(2-naphthoyl)-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4i). Yield 50%, m.p. 169-171 °C. IR (KBr): cm^{-1} 3265 (NH), 1645 (C=O), 1605 (C=N). ^1H NMR (DMSO- d_6): δ /ppm 8.52-7.25 (m, 22H, arom. protons), 5.74 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.10-1.83 (m, 8H, 4CH₂). ^{13}C NMR (DMSO- d_6): δ /ppm 186.66 (C=O), 143.40-125.00 (C=N, arom. carbons), 70.06 (spiro carbons), 43.30 (NCH₃), 27.30, 26.76 (2CH₂). MS: m/z = 780/782 (M^+ , Chlorine isotopes). Anal. for C₄₄H₃₈Cl₂N₈O₂ (781.75): Calcd. C, 67.60; H, 4.90; N, 14.33%. Found: C, 67.50; H, 4.75; N, 13.20%.

1,14-Di(4-chlorophenyl)-3,12-di(2-furoyl)-4,10-dimethyl-1,2,4,5,10,11,13,14-octaazadispiro-[5.2.5.2]hexadeca-2,12-diene (4j). Yield 49%, m.p. 149-151 °C. IR (KBr): cm^{-1} 3270 (NH), 1665 (C=O), 1615 (C=N). ^1H NMR (DMSO- d_6): δ /ppm 7.82-7.11 (m, 14H, arom. protons), 5.64 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.16-1.65 (m, 8H, 4CH₂); ^{13}C NMR (DMSO- d_6): δ /ppm 174.60 (C=O), 143.50-127.77 (C=N, arom. carbons), 71.22 (spiro carbons), 43.07 (NCH₃), 27.30, 26.76 (2CH₂). MS: m/z = 660/662 (M^+ , Chlorine isotopes). Anal. for C₃₂H₃₀Cl₂N₈O₄ (661.55): Calcd. C, 58.10; H, 4.57; N, 16.94%. Found: C, 57.85; H, 4.40; N, 16.85%.

1,14-Di(4-chlorophenyl)-4,10-dimethyl-3,12-di(2-thenoyl)-1,2,4,5,10,11,13,14-octaazadispiro[5.2.5.2]hexadeca-2,12-diene (4k). Yield 51%, m.p. 180-182 °C. IR (KBr): cm^{-1} 3275 (NH), 1655 (C=O), 1610 (C=N). ^1H NMR (DMSO- d_6): δ /ppm 7.89-7.09 (m, 14H, arom. protons), 5.65 (s, 2H, 2NH), 3.05 (s, 6H, 2CH₃), 2.15-1.62 (m, 8H, 4CH₂); ^{13}C NMR (DMSO- d_6): δ /ppm 177.37 (C=O), 143.70-127.38 (C=N, arom. carbons), 71.17 (spiro carbons), 43.11 (NCH₃), 27.10, 26.20 (2CH₂). MS: m/z = 692/694 (M^+ , Chlorine isotopes). Anal. for C₃₂H₃₀Cl₂N₈O₂S₂ (693.68): Calcd. C, 55.41; H, 4.36; N, 16.15%. Found: C, 55.20; H, 4.20; N, 16.00%.

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